

# Anemia is a new complication in Fabry disease: Data from the Fabry Outcome Survey

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## **Anemia is a new complication in Fabry disease: Data from the Fabry Outcome Survey.**

**Background.** The prevalence and causes of anemia among patients with Fabry disease are unknown.

**Methods.** In a cross-sectional study we examined hemoglobin concentrations of patients with Fabry disease using a large international database, the Fabry Outcome Survey (FOS), and analyzed the association of renal function, heart failure, gastrointestinal symptoms, and inflammation, with anemia (hemoglobin <12 g/dL in females and <13 g/dL in males).

**Results.** Anemia was present in 34% of 345 patients with Fabry disease. Median hemoglobin in 158 females was 12.9 g/dL and the median hemoglobin of 187 male patients was 13.2 g/dL. The prevalence of anemia among females was 20%, and among males 47%. Among patients with normal renal function [estimated glomerular filtration rate (GFR) >90 mL/min/1.73 m<sup>2</sup>] and anemia, heart failure [New York Heart Association (NYHA) class II to IV] and/or elevated C-reactive protein (CRP) levels were documented in 82% of patients. Up to 67% of patients with decreased estimated GFR presented with anemia. There was also a trend for lower hemoglobin levels among patients with signs of inflammation (defined by an elevated CRP level). We observed no association of the presence of gastrointestinal symptoms with anemia. Analyses in 53 patients receiving enzyme replacement therapy for up to 2 years, suggest no effect on anemia.

**Conclusion.** The results of this study point to a high prevalence of anemia among patients with Fabry disease that is in most instances related to impaired renal function, heart failure, and inflammation. This finding may be of clinical relevance, because anemia is a major risk factor for patients with kidney

disease, heart failure, or stroke, which are important manifestations of Fabry disease.

Fabry disease is a rare X-linked lysosomal storage disease [1]. Deficient activity of  $\alpha$ -galactosidase A [2] results in accumulation of glycosphingolipids, predominantly globotriaosylceramide, within the lysosomes of multiple tissues and organs [3] and may lead to end-stage renal disease (ESRD), left ventricular hypertrophy, arrhythmia, cerebrovascular disease and, ultimately to premature death. In contrast to many other diseases with X-linked inheritance, many of the heterozygotes are also affected [4, 5]. Fabry disease is a multisystem disorder presenting with impairment of renal function, heart failure, and gastrointestinal disturbances as potential causes for different types of anemia, including renal anemia, anemia of heart failure, or anemia of nutritional deficiencies. Therefore, anemia might be a frequent and important complication of Fabry disease. Furthermore, Fabry disease may also be associated with anemia of chronic disease or inflammation, as reflected by elevated C-reactive protein (CRP) levels. Because anemia is a risk factor for morbidity and mortality among patients with renal [6], cardiac [7–9], or cerebrovascular disease [10], it may be of clinical importance in the majority of patients with Fabry disease. However, data on anemia in Fabry disease are scarce [11] and the prevalence of anemia in this particular patient population is unknown. We therefore analyzed hemoglobin concentration and the prevalence of anemia in patients with Fabry disease enrolled in a large international database, the Fabry Outcome Survey (FOS) [12].

**Key words:** Fabry disease, anemia, renal failure, heart failure, inflammation, enzyme replacement therapy.

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## METHODS

### Design

Hemoglobin concentrations and the prevalence of anemia among all patients with Fabry disease in FOS were examined in a cross-sectional study. In a subset of these patients, we examined anemia during enzyme replacement therapy with agalsidase alfa for at last 2 years.

### FOS

The FOS data base has been approved by the institutional ethical review boards of participating centers, and all patients gave written informed consent. At the time of this analysis (March 2004), FOS contained data on 545 patients (281 males and 264 females) with Fabry disease. On enrollment in FOS, each patient's medical history is documented, including the year of diagnosis of Fabry disease, signs and symptoms of the disease (cerebrovascular, neurologic, psychiatric, ear, eye, cardiac, blood pressure, vascular, respiratory, renal, gastrointestinal, genital, musculoskeletal, dermatologic, endocrinologic, and general symptoms), treatment, demographic details, and family history. All measurements performed routinely in clinical practice (e. g., serum creatinine, proteinuria, hemoglobin, CRP), including follow-up data during enzyme replacement therapy, can be entered in the data base [13]. Laboratory data on iron status, folate levels, and vitamin B<sub>12</sub> levels are not routinely requested in the data base. Data on current therapy with iron and erythropoiesis-stimulating agents were also included in this analysis. Anonymous data are submitted electronically by participating physicians to the central FOS data base.

### A priori definitions

Corresponding to the definition of the world health organization ([http://www.who.int/nut/documents/ida\\_assessment\\_prevention\\_control.pdf](http://www.who.int/nut/documents/ida_assessment_prevention_control.pdf)), we defined anemia in adults as a hemoglobin level of less than 12 g/dL in females and of less than 13 g/dL in males [14]. Glomerular filtration rate (GFR) was estimated using the short Modification of Diet in Renal Disease (MDRD) formula for assessment of renal function [15]. Renal function was classified according to National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [16]. The definition of chronic kidney disease was as follows: stage 1, estimated GFR >90 mL/min/1.73 m<sup>2</sup> (we also included patients with no signs of kidney damage, such as proteinuria or hematuria, in this patient group); stage 2, 60 to 89 mL/min/1.73 m<sup>2</sup>; stage 3, 30 to 59 mL/min/1.73 m<sup>2</sup>; stage 4, 15 to 29 mL/min/1.73 m<sup>2</sup>; and stage 5, <15 mL/min/1.73 m<sup>2</sup> or dialysis. Heart failure [without classifying it according to the New York Heart Association (NYHA)] and presence of gastroin-

testinal symptoms was defined by participating investigators as being present or absent.

### Statistical analysis

Numbers are shown as medians (10th percentile and 90th percentile). Statistical analyses were performed using Spearman's correlation coefficient for ranked data, the chi-square test, Wilcoxon's rank sum test, and the Kruskal-Wallis one-way analysis of variance (ANOVA). Linear associations were assessed by Pearson correlation. In cross-sectional follow-up of hemoglobin concentrations, minimum values for individual patients were used. Longitudinal follow-up of hemoglobin at baseline, 1 year, and 2 years was performed using individual patient's minimum values reported at -6 to +3 months around the start of enzyme replacement therapy for baseline, 9 to 15 months after the start of enzyme replacement therapy, and 21 to 27 months after the start of enzyme replacement therapy, respectively.

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## RESULTS

### Patients

Among 545 patients with Fabry disease registered in FOS as of March 2004, 345 adults (including patients on dialysis and those with kidney transplants; age >18 years) had hemoglobin measurements entered in the data base. The characteristics of the patients are given in Table 1.

Patients in this analysis were recruited from 11 European countries (Germany, 23%; Czech Republic, 11%; United Kingdom, 14%; Switzerland, 10%; Italy, 9%; Belgium, 6%; Spain, 8%; Sweden, 4%; Austria, 3%; France, 7%; and Norway, 5%).

### Hemoglobin concentration and prevalence of anemia

The prevalence of anemia among females was 20% (31) and among males 47% (87) ( $P < 0.05$ ). There was no linear association between hemoglobin concentrations and age in either female or male patients. However, we observed a negative correlation between hemoglobin concentration and the number of organ systems affected by Fabry disease in male patients ( $N = 186$ ) ( $P = 0.006$ ) but not in females ( $N = 144$ ).

Erythropoietin or iron therapy was reported in ten patients. Two female patients received oral iron supplements. Six male patients were on erythropoietin therapy, and another two male patients received oral iron therapy.

**Table 1.** Characteristics of the 345 patients with Fabry disease in the Fabry Outcome Survey from whom hemoglobin concentrations are available

	All patients		Females		Males	
	Median		Median		Median	
	Number	(10th and 90th percentile)	Number	(10th and 90th percentile)	Number	(10th and 90th percentile)
Age at entry <i>years</i>	345	40.1 (23.9 and 58.6)	158	44.5 (25.1 and 64.0)	187	36.3 (23.5 and 53.8)
Age at diagnosis <i>years</i>	320	31.5 (13.0 and 51.0)	140	39 (17.0 and 54.0)	180	26.0 (11.0 and 46.5)
Hemoglobin <i>g/dL</i>	345	13.5 (11.1 and 14.9)	158	12.9 (11.3 and 14.1)	187	13.2 (10.9 and 14.8)
Serum creatinine <i>mg/dL</i>	343	1.0 (0.8 and 1.7)	157	0.9 (0.7 and 1.1)	186	1.1 (0.8 and 2.7)
Serum C-reactive protein <i>mg/L</i>	160	2.7 (1.0 and 10.6)	80	2.3 (0.9 and 9.1)	80	2.9 (1.0 and 14.6)

**Table 2.** Median hemoglobin and proportion of 343 adult patients with Fabry disease with anemia according to estimated glomerular filtration rate class and renal replacement therapy modality

Estimated GFR	Median hemoglobin g/dL (10th and 90th percentile)	Prevalence of anemia	
		Males	Females
>90	13.3 (11.3 and 14.8)	37% (26/71)	26% (7/27)
60–89	13.1 (11.8 and 14.4)	37% (22/60)	17% (16/95)
<60	12.7 (10.6 and 14.2)	67% (20/30)	23% (8/35)
Dialysis	10.7 (8.9 and 12.8)	100% (9/9)	–
Transplant	12.0 (10.2 and 14.6)	63% (10/16)	–

### Hemoglobin and renal function

Both hemoglobin concentrations and GFR estimates were available in 318 adult patients (excluding those who were receiving dialysis or had had a kidney transplant) (Table 2). Three of the dialysis patients were reported to receive erythropoiesis-stimulating agents, four did not receive erythropoiesis-stimulating agents, and concomitant medication was not reported in two patients. The median estimated GFR in patients with a kidney graft ( $N = 16$ ) was 43 (11 and 90) mL/min/1.73 m<sup>2</sup>. The proportion of patients presenting with anemia, according to estimated GFR class, is shown in Table 2. A hemoglobin concentration of less than 11 g/dL, the threshold for treatment with erythropoiesis-stimulating agents, was observed in 118 of 345 patients (34%).

Among patients with an estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup> anemia was more prevalent as compared to patients with an estimated GFR of  $\geq 60$  mL/min/1.73 m<sup>2</sup> [all patients 61% versus 30% ( $P < 0.001$ ); females 35% versus 19% ( $P = 0.13$ ); and males 69% versus 40% ( $P = 0.0005$ )].

By univariate analysis we found no linear association between proteinuria and hemoglobin concentrations ( $r = -0.037$ ,  $P = 0.574$ ).

### Hemoglobin and heart failure

Among 98 patients with an estimated GFR greater than 90 mL/min/1.73 m<sup>2</sup>, median hemoglobin concentration did not differ between the patients ( $N = 54$ ) with heart failure (13.2 (11.3 and 14.6) g/dL) and without [13.6 (11.8 and 14.9) g/dL] ( $P = 0.27$ ). Of the 33 patients with an estimated GFR greater than 90 mL/min/1.73 m<sup>2</sup> and anemia, 19 (58%) had heart failure.

### Hemoglobin and gastrointestinal symptoms

The presence or absence of gastrointestinal symptoms was documented in 332 patients. In females, 58% (85 of 146 patients), and in males 62% (115 of 186 patients) were reported to present with gastrointestinal symptoms related to Fabry disease (NS). Among patients with anemia, 67% (77 of 115 patients), and among patients without anemia 57% (123 of 217 patients) presented with gastrointestinal symptoms (NS).

### Hemoglobin and inflammation

The level of CRP was reported in 169 patients, 56 (33%) had elevated CRP levels. The median hemoglobin concentration was 13.1 (11.3 and 14.5) g/dL in patients with normal CRP levels and 12.8 (10.6 and 14.2) g/dL ( $P = 0.07$ ) in patients with elevated CRP levels. There was no difference in hemoglobin levels in female and male patients with normal versus elevated CRP levels ( $P = 0.14$ ).

Hemoglobin, GFR estimates, and CRP levels were reported in 155 patients; 18 out of 49 patients (37%) with elevated CRP levels, and 25 out of 106 patients (24%) with normal CRP levels, had anemia ( $P = 0.089$ ).

Elevated CRP levels were reported in 33% (36/108) of patients with a decreased estimated GFR and in 28% (13/47) of patients with a normal estimated GFR. The median hemoglobin concentrations in patients with an estimated GFR greater than 90 mL/min/1.73 m<sup>2</sup> with normal ( $N = 34$ ) versus elevated CRP ( $N = 13$ ) were 13.4 (12.3 and 14.8) g/dL and 13.0 (11.3 and 14.6) g/dL, respectively.

Out of the 33 anemic patients with an estimated GFR greater than 90 mL/min/1.73 m<sup>2</sup> CRP levels were available in 17. Of these, five patients had heart failure and an elevated CRP level, nine patients had heart failure and a normal CRP level, and three patients had a normal CRP level and no heart failure. Thus, in 82% of patients with an estimated GFR greater than 90 mL/min/1.73 m<sup>2</sup>, anemia may be related to heart failure, inflammation or both.

### Hemoglobin concentrations during enzyme replacement therapy

During enzyme replacement therapy with agalsidase alfa (Replagal<sup>TM</sup>) (TKT Europe) (0.2 mg/kg body weight every 2 weeks intravenously) [17] in 53 patients (15 females and 38 males) the median hemoglobin

concentration was 13.5 (11.8 and 14.7) g/dL at baseline, 13.3 (11.7 and 15.0) g/dL after 12 months, and 13.5 (12.2 and 14.6) g/dL after 24 months ( $P = 0.9$ ). The prevalence of anemia was 26% at baseline, 30% at 1 year, and 23% at 2 years of enzyme replacement therapy.

## DISCUSSION

This study provides evidence for a high prevalence of anemia among adult patients with Fabry disease. Major causes of anemia are impaired renal function, heart failure, and inflammation. Among patients with an estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup>, up to 69% presented with anemia. Of note, up to 40% of patients with an estimated GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> were also anemic. Of the anemic patients with a GFR estimated to be normal, 82% presented with heart failure and/or inflammation.

The major cause of anemia in patients with renal disease is erythropoietin deficiency and insufficiency of iron [18]. In chronic kidney disease, hemoglobin levels decline in parallel with the decrease in GFR [19], finally resulting in severe anemia in about 95% of individuals with ESRD and dialysis treatment. Considering a cut point of GFR of 60 mL/min/1.73 m<sup>2</sup> that has been previously suggested to distinguish moderate chronic kidney disease (GFR <60 mL/min/1.73 m<sup>2</sup>) from better renal function (GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>) [16], anemia was reported in 61% and 30% of our patients, respectively. These numbers are in stark contrast to results of a large study of 13,716 participants in the prospective Atherosclerosis Risk In Communities (ARIC) Study, where anemia was reported in 12.2% of individuals with an estimated GFR of <60 mL/min/1.73 m<sup>2</sup> and in 8.7% of individuals with an estimated GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> [10]. Thus, the present study suggests that anemia is more prevalent in either Fabry patients with advanced chronic kidney disease or in Fabry patients with better renal function as compared to a community-based population.

Given this excess prevalence of anemia in our large population of patients with Fabry disease, potential other causes of anemia, such as heart failure or inflammation, deserve consideration. In patients with heart failure, anemia, related to an increased abundance of several cytokines that impair erythropoiesis, may be of considerable importance [20]. In this context, several large studies have demonstrated a high prevalence of anemia among patients with heart disease [20]. Recently, a new concept has been developed that relates heart failure, kidney failure, and anemia in a vicious circle, where each of the three symptoms has a negative effect on the other two [21]. This vicious circle has been described as the cardio-renal-anemia syndrome, and is applicable to Fabry disease, where heart failure and kidney disease play a prominent role.

Systemic disorders such as Fabry disease may also result in the hypoproliferative anemia of chronic dis-

ease, which is commonly normochromic or mildly hypochromic anemia. The major cause of the anemia of chronic disease is a disturbance of erythropoiesis due to reduced production of, and sensitivity to, erythropoietin [22]. Inflammation, as reflected by elevated CRP levels, may also be related to infection and can adversely affect hemopoiesis by many mechanisms in addition to nonspecific suppression of erythropoietin production and erythropoiesis through the production of inflammatory mediators [23]. A characteristic of the anemia of chronic disease is an abnormality of iron distribution as reflected by low levels of iron in serum and decreased transferrin saturation despite adequate storage, but with a reduction of iron granules in marrow erythroblasts [22–24].

Among the patients with Fabry disease in the present study, a high proportion of anemic individuals with a normal estimated GFR showed heart failure and/or inflammation, pointing to a significant role of the anemia of chronic disease in this specific patient group. Although the cause of heart disease in Fabry disease is well established, the reason for the high prevalence of elevated levels of CRP among patients with Fabry disease is currently unknown. Remarkably, the proportion of patients with elevated CRP levels was high among individuals with a decreased estimated GFR and also in patients with a normal estimated GFR. Therefore, inflammation may be an additional contributor to anemia not only in patients with impaired renal function. Notably, we also observed a negative correlation between hemoglobin concentration and the number of organ systems involved in male patients, but not in females. This finding may be related to the more severe presentation of disease among male patients and may point to a substantial role in the anemia of chronic disease in Fabry disease. Thus, the high frequency of renal failure, heart failure, and inflammation in patients with Fabry disease makes this population so unique for developing anemia.

Gastrointestinal symptoms are frequently reported in patients with Fabry disease and represent a potential cause for micronutrient malnutrition resulting in anemia of iron, folate, or vitamin B<sub>12</sub> deficiency. In our patient population, however, the proportion of patients with gastrointestinal symptoms did not differ between anemic and no anemic individuals.

In the general population, anemia is an important risk factor for heart failure, myocardial infarction, and stroke [7–10]. Therefore, the present study paves the way for future analyses that should examine the effect of anemia and its correction on morbidity and mortality in patients with Fabry disease. These patients show an excess mortality compared with the general population, with death occurring on average at 50 years of age in males [11]. Life expectancy is also significantly impaired in females [4].

Enzyme replacement therapy for Fabry disease was introduced into clinical practice several years ago [17, 25] and may improve the morbidity and premature mortality

associated with the disease. In our analysis, hemoglobin levels and the prevalence of anemia did not change during a 2-year period of enzyme replacement therapy that may be related to the stabilization of kidney function or heart disease during enzyme replacement therapy.

The limitations of the present study are the lack of reporting iron status or folate and vitamin B<sub>12</sub> levels in the FOS data base. Information on therapy with erythropoietic agents, iron or vitamins is not specifically requested to be entered in the database and is therefore probably not complete. Thus, we cannot exclude a major role of micronutrient deficiency on anemia in this cohort of patients with Fabry disease. Importantly, iron deficiency that may contribute to anemia in a substantial proportion of our patients was not considered in our analysis. We have not performed bone marrow analyses in our patients and we are not aware of any other study examining the morphology of the bone marrow in patients with Fabry disease. Therefore, we cannot reject bone marrow accumulation of Gb3 as potential cause of anemia in our study population. Furthermore, assessment of renal function using the MDRD GFR formula has not been formally examined in patients with Fabry disease. In addition, the methods used for measurement of serum creatinine in the different centers participating in FOS vary due to lack of international standardization of creatinine determination in clinical laboratories [26, 27]. Therefore, the stage of chronic kidney disease, as estimated according to the K/DOQI guidelines, may be missclassified in some of the patients.

## CONCLUSION

The results of this study point to an excess prevalence of anemia in patients with Fabry disease. This finding may be of considerable importance, as anemia is a risk factor for patients with kidney disease, heart failure or stroke, which are important manifestations of Fabry disease. Furthermore, we have demonstrated the potential of a large international database for identifying a hitherto unknown and underrecognized complication of a rare monogenic disease.

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